

REMARKS

By entry of this Amendment, claims 1-18 are pending in the present. Reconsideration is respectfully requested.

Claim Rejections Under 35 USC § 103

Claims 1-18 are rejected under 35 USC §103(a) as allegedly being obvious in view of a combination of Kingston US 5,470,866, Gennari et al. I (*Pure & Appl. Chem.*), or Gennari II (*J. Braz. Chem. Soc.*) or Chen CA 123:112445. Applicants traverse.

The Methods of the Cited References and the Present Methods of Claims 1-12 Recite Completely Different Processes to Convert Cephalomannine to a Taxane.

The presently claimed processes of claims 1-12 recite and require initial oxidation steps.

The presently claimed processes of claims 1-12 for converting cephalomannine to a taxane utilize oxidation as an initial process step. Specifically, oxidation process steps are recited, namely, through aziridine (claim 1) or epoxy (claim 10) intermediates, or through nitrosation (claim 7). In the claim 4 process, cephalomannine is converted directly to the amine intermediate.

There is no prima facie case of obviousness presented, as the references cited, whether considered independently or in combination, fail to teach or suggest such initial oxidation of cephalomannine as recited in claims 1-12.

The '866 patent neither teaches nor suggests a process where cephalomannine to a taxane utilizing oxidation as an initial process step. Instead, the '866 discloses a method of converting cephalomannine to either paclitaxel or docetaxel by initially hydrogenating the cephalomannine. Subsequent steps proceed via a primary amine at C(3'). Therefore, the '866 patent is teaching a person of ordinary skill in the art that to convert cephalomannine to paclitaxel one must first perform a reduction reaction (i.e., hydrogenation as disclosed in the '866).

Neither of the Gennari references cited nor the Chen reference, individually or in combination with the '866 patent, make up for this deficiency of the '866 patent disclosed process. Both Gennari references disclose the stereochemistry of chiral boron enolates derived from α -oxy substituted thioacetates. In particular, Figures 6 and 7 examine the relative

production of a-haloacetates with different stereochemistries. The Gennari references also discuss the production of paclitaxel by a semi synthetic pathway, using imine addition of thioester derived boron enolates. However, there is no disclosure of converting cephalomannine to paclitaxel or docetaxel in either reference.

The disclosure in Chen is even further removed from claimed processes of the present invention. Chen discloses the synthesis of C-4 aziridine bearing paclitaxel analogues. The present process does not recite any such substitution at C-4. Besides not making up for the deficiencies of the '866 patent disclosure in teaching or suggesting the claimed processes, Chen is essentially completely unrelated to the presently claimed processes.

There is no prima facie case of obviousness presented, as the references cited are not properly combinable.

Even if, *arguendo*, the proposed combination of references taught the claimed processes (which they clearly do not), the proposed combination is improper as there is no reasonable expectation of success with such a combination. As the Examiner knows, the Examiner's proposed substitution of a process step taught in the secondary references to replace the entire process disclosed in the primary reference '866, the examiner must evidence that such a substitution of process steps would be "obvious to try." To be "obvious to try" the switching of chemical process steps must have "a reasonable expectation of success." MPEP § 2143 E; § 2145 B; § 2143.02; and § 2143.02 II. The chemical arts, and especially complex organic syntheses, are innately unpredictable and the Examiner shows no evidence supporting a belief that one of ordinary skill in the art would believe that the proposed substitution of method steps of Gennari or Chen for the disclosed process steps in the '866 patent would result in the production of the paclitaxel disclosed in the '866 patent. The Examiner is using impermissible hindsight to combine references to achieve the claimed invention.

Additionally, the Examiner's assertion that the intermediates recited in the present processes are inherently formed by the Examiner's proposed combination is unsubstantiated and incorrect. Furthermore, the Examiner's assertion that the "mix[ing] and match[ing] of different steps such as ring closure first, then condensation" is not only irrelevant to the claimed processes, the Examiner shows no evidence supporting the assertion that the recited process steps are "conventional." For at least these reasons, the proposed combination of references is improper

and does not present a *prima facie* case of obviousness. Lastly, prior art references must clearly and unequivocally disclose the claimed invention or direct those skilled in the art to the invention without any need for picking, choosing and combining various disclosures not directly related to each other by the teachings of the cited primary reference. *In re Arkley*, 455 F.2d 586, as cited in *Sanofi-Synthelabo v. Apotex*, 2007-1438 (Fed. Cir. Dec. 12, 2008).

Accordingly, for at least the reasons set forth above, the art of record, considered independently or in combination, neither teach nor suggest the recited claims 1-12 processes.

The Methods of the Cited References Do Not teach or Suggest the Preparation of Paclitaxel and Docetaxel from Cinnamoyl Halide or Preparation of Docetaxel from Cephalomannine as Recited in the Methods of Claims 13-18.

There is no prima facie case of obviousness presented, as the references cited, whether considered independently or in combination, completely fail to teach or suggest (or even mention) the preparation of paclitaxel and docetaxel from cinnamoyl halide (as recited in claims 13-17).

There is also no prima facie case of obviousness presented as to claim 18, as the references cited, whether considered independently or in combination, completely fail to teach or suggest (or even mention) the preparation of docetaxel from cephalomannine.

Accordingly, claims 13-18 are allowable over the art of record.

Obviousness-type Double Patenting Objection:

Claims 1-18 are rejected on the ground of non-statutory obviousness-type double patenting as allegedly being unpatentable over claims 17-18 of U.S. Patent No. 7,202,370 in view of Gennari et al. I (*Pure & Appl. Chem.*), or Gennari II (*J. Braz. Chem. Soc.*) or Chen CA 123:112445. Applicants traverse.

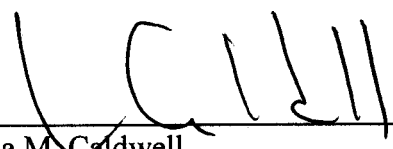
The '370 patent relates to the semi-synthesis of paclitaxel intermediates from 9-DHB. This is different from the processes claimed presently. The Examiner alleges that claims 17 and 18 of the '370 patent deem the presently claimed invention obvious. In claims 17 and 18 of the '370 patent the C(2') position of the starting material is unsubstituted. Therefore, the starting material is neither cephalomannine nor BACC III. Furthermore, the starting material does not have a hydroxy group at C(2'), as required in the corresponding side chain in paclitaxel. The

same holds for claim 18 where C(2') is substituted by a diazo group. Therefore, the '370 patent neither teaches nor suggests the presently claimed methods. The further references cited by the Examiner do not make up for the deficiencies in the '370 patent. Accordingly, the rejection should be withdrawn.

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

By



Lisa M. Caldwell
Registration No. 41,653

One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, Oregon 97204
Telephone: (503) 595-5300
Facsimile: (503) 595-5301